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**PREVENTION OF CLINICAL OUTCOME AFTER
IMPACTED THIRD MOLAR SURGERY IN CORRELATION WITH
BLOOD FIBRIOLYTIC ACTIVITY**

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Abstract

The aim was to investigate how impacted third molar surgery, as psychophysical and operative trauma; influence the response of blood fibrinolytic system. Examined group included 50 healthy subjects with impacted third molars and 45 subjects, blood donors, as a control group. Influence of the operative interventions over parameters of blood fibrinolytic system (t-Pa and PAI-1) were examined prior the procedures and immediately after. Values of blood pressure and pulse were notified to evident physical reflections of the stress. Clinical outcome after first, second and seventh day included changes like edema, hematoma, pain and dry socket. Impacted third molar surgery, as a stress factor, had influence and affects the fibrinolysis through the effect upon the pro-activators and inhibitors of the fibrinolytic system, and the severity of the clinical outcome after operative third molar surgery. Parameters of fibrinolytic system - t-PA and PAI-1 can be the most sensitive markers of reaction to oral surgical stress.

Key words: impacted third molar, oral surgery, fibrinolytic system, stress.

Introduction

The scientific investigations of many authors had the aim to evaluate the influence of the surgery stress and the operative trauma after oral surgery interventions and some of them after impacted third molar surgery over certain parameters of coagulation and the blood fibrinolysis [4-8, 27].

According to Grand [9] the acute physical stress as the major surgery is the insulin induced hypoglycemia and the physical exercises are connected to the acute increase of the concentration of the factor VIII in the circulation as well as increased fibrinolytic activity of the blood. The mechanisms that are included in the production of these answers are partly under hormone control and it's obvious that the changes are mediated by the neurohormones adrenalin and arginine vasopressin.

Kehlet [14] emphasized that the operative surgical trauma and modified effects of the pain are the reason for the start of possible complications such as infections and hemorrhage. Especially as a consequence of the activation of some humoral substances: prostaglandin, kinin, leukotren, interleukin-1, as well as the tumor necrotic factor, it's possible mentioned complications to be created. [3]. The synthesis and the secretion of the thromboplastin, antigen activity of F VIII: factor v. Willebrand, then activity of the inhibitor of the plasminogen -1 (PAI-1) activator decrease production and secretion of the tissue type plasminogen activator (t-PA) at the same time.

In the modern scientific book's knowledge[2,5] there is an elaboration of accidentally discovered cases with prolonged bleeding after finished extraction [18]

when often rare deficits of some factors of coagulation [18,19,24] or of the inhibitors of the fibrinolysis [12-16,21,26,25] are discovered.

The basic aim of this research was to determine whether the operative interventions, more precisely- impacted third molars surgery, as the psycho-physic and the operating trauma influence behavior of the fibrinolytic blood system. The second aim was to determine the correlation of the values of the level of the fibrinolytic system activators and inhibitors and the clinical outcome in the post oral surgery period.

Material and Methods

These researches covered 50 examinees, both male and female, on age between 25 - 45, healthy patients. According to the data of anamnesis, clinical and radiographic examination, indications for operative extraction were performed (impacted third molars in the lower jaw with mesio angular position). The surgical procedures were done for 35-40 min, and the operative trauma was similar in the examinees, according to the operative protocol. The interventions in the examined group were realized during the morning hours at the Department for Dental Medicine, "Goce Delcev" University_Stip, R. Macedonia.

The control group was consisted of 45 examinees-blood donors, both male and female, at age between 25 –35, healthy patients, without any dental intervention, as stress factor.

All examinees agreed to be included in our research.

Venous blood was taken before and after the surgery treatment from the examined group and also, from the control group. The blood samples were instantly distributed for laboratory analyses to the Laboratory of Blood Transfusion, at the Clinical Hospital –Stip, Macedonia. There was a selective determination of the activator of the fibrinolytic activator of the plasminogen - tissue-type plasminogen activator - t-PA antigen; (t-PA-Ag) INNOTEST t-PA and of the inhibitors of the activators of the plasminogen - antigen (Plasminogen activator inhibitor -1-antigen; PAI-1-Ag), with INNOTEST PAI-1 (Biopol Trinity Company, Ireland). Both tests are immuno-enzymatic analysis - MIKRO-ELISSA method, with double antibody or sandwich method where the antigen is inserted.

The values of the blood pressure and the pulse, as objective parameters of the physical reflection of the operative stress were recorded in four phases: before the interventions, after the application of the local anesthesia, during the intervention and at the end of it. With all examinee the presence of fear according to the subjective statements was recorded.

The control visits were done at the first day, second and seventh day after the interventions, recording the presence of edema, hematoma, pain, dry socket and prolonged bleeding.

For statistics elaboration and analysis of the obtained data, the statistics program "Statistica" was used.

Results

The distribution of the values for t-PA and PAI-1 for the examined group before and after the operative intervention is showed in the figure 1.

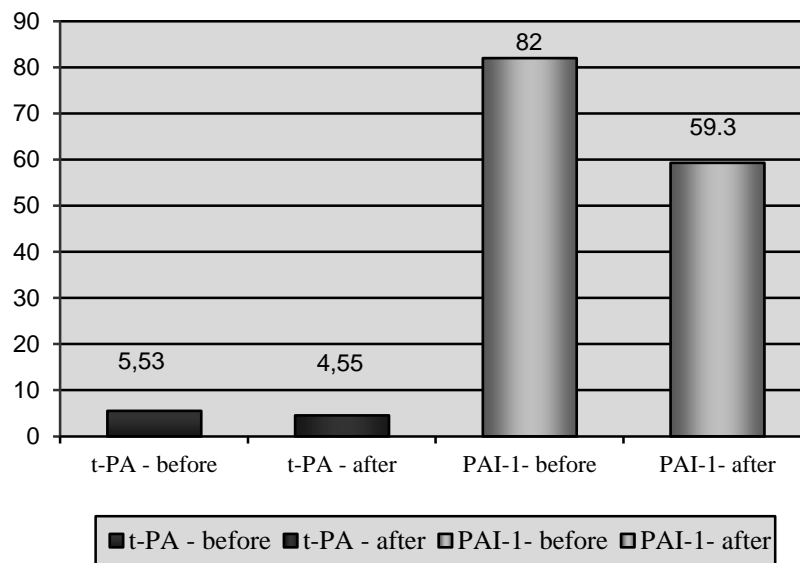


Figure 1. Values of t-PA and PAI-1 before and after the operative interventions of impacted third molars

The value of t-PA after the surgical extractions (4.55 ng/ml) is decreased comparing to the value before them (5.53 ng/ml); analyzed with "t" test showed statistically significant difference ($t = 3.29$; $p < 0.01$). The value of PAI-1 after the surgical extractions (59.3ng/ml) is significantly decreased comparing to the average value of PAI-1 before the interventions (82ng/ml). Their analysis showed statistically significant difference ($t = 2.59$; $p < 0.05$).

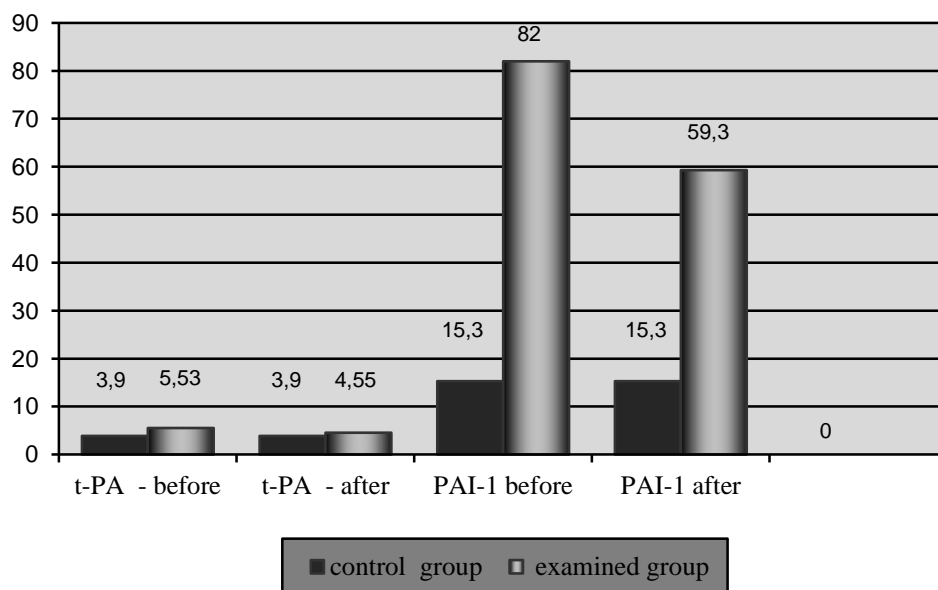


Figure 2. Values of t-PA and PAI-1 before and after the operative interventions of impacted third molars inn the examined group in correlation with the control group

The values of t-PA and PAI-1 before and after the intervention for the examined group are significantly higher comparing to the same parameters for the control group and the analysis of the average values showed statistically significant difference in all of the examined relations (t-PA – contr. / t-PA- before $t=4.26$, $p<0.01$; t-PA – contr. / t-PA - after $t=2.21$ $p<0.05$; PAI-1-contr. / PAI-1-before $t=7.89$, $p<0.01$; PAI-1-contr. / PAI-1- after $t=6.60$, $p<0.01$; figure 2).

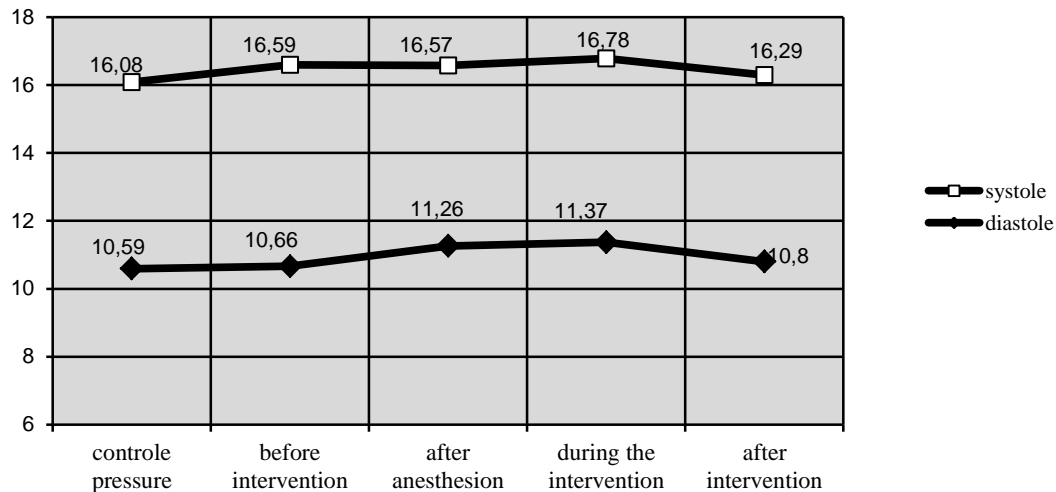


Figure 3. Values of systole and diastole blood pressure in the examined group

The average values of the systole and diastole blood pressure for the examined group are shown on figure 3. The analysis of the average values of the systole pressure between the examined and the control group in all of the researching phases showed that there is no statistically difference ($t = 1.77$; 0.09 ; 0.66 ; 1.47 and $p<0.05$).

The analysis of the average values of the diastole pressure between the examined and the control group in all of the researching phases showed that there is no statistical difference ($t = 0.25$; 0.40 ; 1.9 and $p<0.05$) except in the relation before the intervention / after the anesthesia ($t = 2.76$, $p<0.001$).

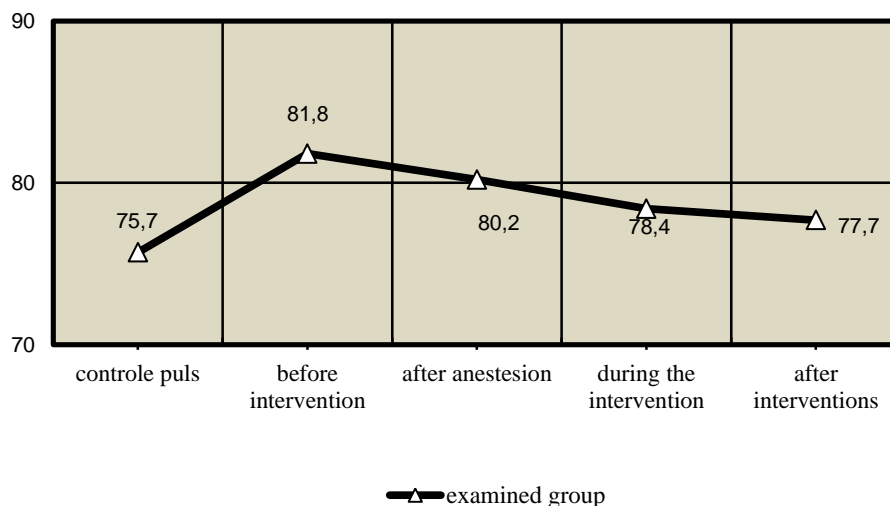


Figure 4. Values of the pulse in the examined group

The average values of the pulse at the examined group are shown on figure 4. The analysis of the average values between the examined and the control group showed high statistical difference in the relation control pulse / before intervention ($t = 4.33$, $p < 0.001$). In the rest of the researched relations it was shown that there is no significant difference ($t = 0.33$; 0.87 ; 0.95 and $p < 0.05$). The subjective statements for the presence of fear among the examinees with operative extractions of impacted third molars are shown on table 1. Before the extractions, 18 of the examinees (32.5%) had no fear, while 32 (67.5%) felt fear, and 27 examinees (55%) felt fear during the intervention.

Table 1. Presence of fear before and after the interventions in the examined group

fear	n = 50			
	Before the interventions	%	During the interventions	%
absence	18	32.5	23	45
presence	32	67.5	27	55
a little	12	30	9	22.5
a few	7	17.5	9	22.5
a lot	8	20	1	2.5
increasing	0	0	3	7.5
differences	Chi Sqr.=1.74			

Table 2. Presence of clinical outcome after operative extractions of impacted third molars in the examined group

(n = 50)	First day				Second day				Seventh day			
	oedema		hematoma		oedema		hematoma		oedema		hematoma	
	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%
absence	24	47.5	50	100	35	75	50	100	50	100	50	100
presence	26	52.5	0	0	15	25	0	0	0	0	0	0
	pain		dry socket		pain		dry socket		pain		dry socket	
	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%
absence	17	42.5	40	100	27	55	35	75	50	100	40	87.5
presence	33	57.5	0	0	23	45	15	25	0	0	10	12.5

Table 3. Spearman coefficient of correlation between t-PA and PAI-1 after the interventions and the parameters of the control examinations in the examined group

parameters	Spearman R.	p
t-PA after interv. / edema –first day	- 0.049	p = 0.76
t-PA after interv. / edema –second day	0.043	p = 0.79
t-PA after interv. / edema - seventh day	/	/
t-PA after interv. / hemat. -first day	/	/

t-PA after interv. / hemat. - second day	/	/
t-PA after interv. / hemat. - seventh day	/	/
t-PA after interv. / dry socket. - first day	/	/
t-PA after interv. / dry socket - second day	0.005	p = 0.97
t-PA after interv. / dry socket - seventh day	0.101	p = 0.53
PAI-1 after interv. / edema - first day	- 0.357	p = 0.02
PAI-1 after interv. / edema - second day	- 0.233	p = 0.14
PAI-1 after interv. / edema - seventh day	/	/
PAI-1 after interv. / hemat - first day	/	/
PAI-1 after interv. / hemat - second day	/	/
PAI-1 after interv. / hemat. - seventh day	/	/
PAI-1 after interv. / dry socket - first day	/	/
PAI-1 after interv. / dry socket - second day	- 0.32	p = 0.04
PAI-1 after interv. / dry socket - seventh day	- 0.167	p = 0.30

After the first and second day from the operative extractions of impacted third molars, no prolonged bleeding was seen among the examinees. The data of the examined group about the appeared edema, hematoma, pain, alveolitis during the control investigations after the first, second and seventh day are shown on table 2.

With the Spearman coefficient of correlation, the linear connection between the values of t-PA and PAI-1 was determined after the operative extractions of impacted third molars with the parameters from the control examinations. The coefficients of correlation shown on table 3 showed modest connection. There is a domination of the values of the relation of PAI-1 after / edema first day; PAI-1 after / edema second day; PAI-1 after / alveolitis seventh day; t-PA after / alveolitis seventh day.

Discussion

This study had an attempt to give an answer to the question: whether the oral surgical interventions of impacted third molars, similar to the intensity of the surgical trauma, done under local anesthesia at the healthy persons (with intact system of hemostasis) could cause changes to some parameters of the haemostatic, in other words in the fibrinolytic blood behavior.

Having on mind the complexity of the system for hemostasis, our mean was that the research enabled us to obtain a real clinical evaluation of the physiological activity of the fibrinolytic system of the blood during impacted third molars surgical extractions.

The knowledge about the local haemostatic balance is significantly increased with the examination of the patients with congenital and acquired defects of the coagulation system [12, 15, 16, and 21]. According with this, the knowledge of the specific type and

the strength of the prolonged bleeding are crucial for the planning of a safe and suitable oral surgical treatment, only with an aim to minimize the risk of prolonged bleeding [4].

In the researches of Emeis, Prowse & MacGregor, Rånby & Brandström [2], it's stated that the circulation at individuals that aren't under stress, t-PA circulates as a complex with PAI-1. It is indicative in the finding that in the normal plasma in a still condition, the bigger part or the whole t-PA is present in the complex with PAI-1. The stimulations of the physical activities lead to release of t-PA, and then t-PA freely circulates and temporarily stops the PAI-1 effect. The stress, pain, physical exercises, adrenaline injecting or venous occlusion have been known for a long time as conditions that result with significant increase of the activators' level of the plasminogen [20,25,28]. Mullertz, Gram, Aoki in the presented researches of Sprengers, Kluft et al. [25] report identical results. It's said that the amount of t-PA in the blood could be acutely increased with stimulants as the radiation, trauma and surgical intervention were. That could be explained with several mechanisms: increased synthesis of t-PA, decreased purity of t-PA and exit of t-PA from the cellular and extra-cellular depots.

All those emphasize the acute changes of the t-PA level. The activation of the plasminogen with t-PA is strengthened by the fibrin that creates matrix. In that mean, t-PA and the plasminogen are in suitable position including the confirmation changes that make the activation suitable. During the resolution of the fibrin, the connection of the plasminogen and t-PA with the partly degraded fibrin is strengthened, enabling highly efficient fibrinolysis against the decreased concentrations of the involved components. At the same time, t-PA appears in complex with the C1- inhibitor and α_2 – MG [4, 7, and 18].

Congenital plasminogen activator inhibitor-1 (PAI-1) deficiency is an extremely rare disorder characterized by a bleeding diathesis due to hyperfibrinolysis as a result of decreased PAI-1 activity [12, 15, 16, 27]. Takahashy et al. [26] and Tanimura et al. [27] present cases with partial quantitative deficit of the plasminogen activator inhibitor - 1 (PAI-1), of the members of several families in Japan that had prolonged bleeding episodes after trauma and teeth extractions.

The characteristic disorders of the fibrinolysis with them were: shortened time of the euglobulin lisa, low level of PAI-1 activity with low levels of the PAI-1 antigens in the plasma and serum. For these patients it was used 5% tranexemic acid, as a solution for mouth washing in order to decrease the bleeding during and after the extraction. The authors [12,15,16,23,26,27] considered PAI-1 deficiencies to be the likely aetiology of the congenital bleeding diatheses in the present cases with prolonged bleeding episodes after trauma and teeth extractions.

The results from our statistical analysis undoubtedly show that during the surgical extractions at the examined group there were changes of the values of the researched parameters from fibinolytic system. Further more, there is a need to mention that all higher or lower values of the examined parameters from the fibrinolysis at both of the examined groups, are not enormously higher or lower. They are in the frames of the physiological, referent limits.

Kaličanin and Lečić – Toševski [11] emphasize the Selye's concept. They considered that the stress reaction is always same i.e. stereotypical, no matter what

stressor is. Every phase of the stress is accompanied by biological modifications and rather stereotypical and characteristic clinical manifestations caused by oscillations of the regulator biological mechanisms.

But, the most comprehensive researches [1, 17, 18, 22, and 29] showed that the stress reactions couldn't be described as stereotypical changes and processes. Most of the authors [17, 20, 16, and 27] agree for one that the human, psychological, biological and social nature is unique and undivided. So the stress in a best and most correct way can be defined as a whole psycho-socio-biological answer of the organism towards the action of any stressor that attacks its homeostasis.

Raikkonen et al. [21] researched the effect of the chronic stress comparing to the t-PA and PAI-1 at 69 healthy men at average age. The findings confirm the hypothesis that the chronic stress creates changes in the fibrinolytic system and suggests that the fatness, level of the insulin and triglycerides are in a very close correlation to the fibrinolytic parameters, in other words increased synthesis of t-PA and PAI-1.

The measurements of the blood pressure and the pulse in the given researches of the shown results and distributions of the average values of the systole and diastole blood pressure don't show any bigger differences. Before the intervention, after the anesthesia, during and at the end of the extractions and the analysis of the average values of the systole pressure, statistically significant difference is not seen in all of the analyzed relations; while the average values of the diastole pressure showed statistically significant difference in certain analyzed relations. The analysis of the average values of the pulse showed statistical difference in some analyzed relations.

Dimova [4] emphasized that the stress is more present at the examinees with extractions against the examinees with surgical interventions. This is also confirmed subjectively with the personal statements of the examinees and objectively through the values of the diastole pressure and the pulse. These findings are according to pre-surgical psychological preparation of the examinees before the oral surgical interventions, which significantly helps in decreasing of the stress before and during the surgical interventions, then in the appearance of the fear before the extractions.

Our findings for the presence of edema, hematoma in the period after the intervention show that there is a moderate correlation of the same ones with the values of t-PA and PAI-1 after the operative orals surgical extractions of impacted third molars. In the period after the extractions no hemoridge was noticed, which was confirmed at the control examinations. This finding is normal as the examinees are with intact system of hemostasis.

Conclusions

The examinations from this study can determinate precisely the fibrinolytic blood activity during the oral surgery interventions of impacted third molars (mesioangular positions) and emphasize the following conclusions:

1. Operative extractions of impacted third molars had influence on the fibrinolysis by releasing of the pro-activators and the inhibitors of the fibrinolytic system. Immuno-enzymatic test of the fibrinolytic activity showed increased values of t-PA before the operative intervention comparing to the values of the control group

and some decrease after the operative procedures. These values are in correlation with the increased values of PAI-1.

2. The values of the examined vital parameters, the blood pressure and pulse, as well as from the data for presence of the stress before and during the operative interventions, made a clear view for stress reaction on the examinees. The changes of the values of the diastole blood pressure and the pulse confirm the psychological dimension of the oral surgical interventions of impacted third molar surgery.
3. The correlations of the fibrinolytic system parameters with the control examinations parameters (edema, hematoma, pain and dry socket) showed that there were correlation between the values of t-PA and PAI-1 after the operative procedures, which implicate the clinical outcome of the post oral surgery period. Parameters of the fibrinolytic system, t-Pa and PAI-1, can be used as the most sensitive markers of reaction to surgical stress during the oral surgical interventions of impacted third molars.

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